Yale University Institutional Review Boards

IRB Policy 420 Data and Safety Monitoring

Responsible Office	Office of Research Administration	Effective Date:	May 31, 2007
Responsible Official	Institutional Review Board Executive Chair	Last Revision:	11Dec2017

Scope

This policy describes requirements related to data and safety monitoring of research, thereby contributing to the safety and well-being of research subjects who are a part of the proposed research protocol. This policy applies to all investigators at Yale or its research affiliates who conduct human research.

Policy Statement

All non-exempt human research protocols submitted to the Institutional Review Board (IRB) for review must include an explicit Data and Safety Monitoring Plan (DSMP). The plan must detail how the Principal Investigator (PI) will conduct monitoring of human research subjects' data and safety commensurate with the risks associated with their participation in Yale research. In addition, for multi-center clinical trials in which the Yale (or research affiliate) PI serves as the overall PI, the DSMP must include a detailed plan describing how the PI will conduct data and safety monitoring for the subjects at all external sites.

The formation and use of a Data and Safety Monitoring Board (DSMB) may be required by the IRB in certain circumstances depending on the level of risk to research subjects, when a real or potential interest of a study investigator or the University, poses, or may pose, a significant conflict of interest or when the study involves a new intervention whose risk levels are uncertain. When a DSMB exists, the DSMP must include plans for submitting DSMB reports to the IRB and other research oversight committees.

The IRB is responsible for evaluating the appropriateness of the DSMP when it performs initial and continuing protocol reviews in accordance with IRB Policy 100 and 45CFR §46.111(a)(6) and 21CFR §56.111(a)(6) as applicable.

Reason for the Policy

Data and safety monitoring is considered to be an essential component in the protection of human research subjects. Investigators and the IRB must ensure that an adequate and appropriate data and safety monitoring plan is proposed and approved prior to the commencement of any human research. By doing so, both the investigators and the IRB ensure that any events or problems which may present a risk to study subjects are monitored, reported and resolved. By examining the accruing data for indications of benefits or harm (including physical, psychological, economic or social harm), the investigator, the IRB or the DSMB can assess new risks and determine if the study should progress, be altered for more protections, or be terminated.

Definitions

Adverse Event
An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention.

Data and Safety Monitoring Board or Committee (DSMB/DSMC)
A group charged by the sponsor, investigator, or steering committee of a study with protecting subject safety by examining the accruing data for indications of benefit or harm. The DSMB/DSMC makes a judgment as to whether the trial should continue. The DSMB/DSMC usually looks at global data, as investigators forward all adverse event reports and safety data to a data coordinating center, which compiles the data for the DSMB/DSMC to review at predefined intervals. Data presented to the DSMB/DSMC is either completely unblinded, or categorized by treatment arm. As such, the DSMB/DSMC is able to determine whether a clear effect exists in one arm of the study versus the other(s).

Data and Safety Monitoring Plan (DSMP)
A plan, tailored to a particular protocol, that describes who has the responsibility to monitor study data and at which frequency study data is monitored to ensure the safety of human subjects and integrity of study data.

Related Events
These are events that are possibly, probably, or definitely caused by the research procedures or related to research participation.

Reportable Adverse Event
An adverse event that must be reported to the IRB because it is all of the following:

1. Serious or life-threatening; AND
2. Unanticipated (unexpected) OR anticipated but occurring with a greater frequency than expected; AND
3. Possibly, probably or definitely related to the drug/device/intervention.

Risk

The probability and magnitude of harm occurring to a research subject including physical, psychological, social, reputational or financial harms or criminal or civil liability.

Risk associated with participating in a study can be categorized as:

Minimal Risk
The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR §46.102(i), 21 CFR §50.3(k)). Examples may include blood draws of small volumes for research purposes, the collection of biological specimens for research purposes by noninvasive means, the collection of data from medical records, and most research employing surveys, interviews, or focus groups.

Moderate Risk
Risk that is greater than minimal, but not high and where there is adequate surveillance and protection to minimize risks and discover adverse events promptly. Examples include insulin clamp studies, Phase II and some Phase III trials, and some biopsies.

High Risk
Studies that pose potential significant harm to a subject because of the nature of the study or because there is significant uncertainty about the possible occurrence or nature of the risks. Examples may include most Phase I investigational drug or device trials that aim to establish a safety profile, and that have not yet been conducted in humans (so-called First in Man Trials – FiMT).

Serious Adverse Event
Any adverse event that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Unanticipated Problem or Event
Problems, risks or events that occur during the conduct of the research, but were not expected and therefore are not cited in the written protocol, the consent form(s) or the Investigator's Brochure.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)
Any incident, experience or outcome that:

1. Is unexpected (in terms of nature, severity, or frequency) given the research procedures and protections described in the protocol and the characteristics of the participant population; AND
2. Suggests that the research participation places the participant(s) or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized; AND

3. Is possibly, probably or definitely related to the participant's involvement in the research.

Policy Sections

420.1 Required Elements of the DSMP

The DSMP must document the procedures and means to protect the welfare and safety of subjects and to protect the integrity of the data. When the study sponsor is performing data and safety monitoring activities, the Yale investigator must provide a brief plan that describes how the local monitoring responsibilities will be integrated into the sponsor's DSMP and accomplished by the Yale Principal Investigator (PI) and how the IRB reporting requirements will be met.

All DSMPs must include:

- A description of the monitoring of the progress of the study, the safety of subjects, data accuracy and assuring protocol compliance.
- A description of the mechanism and timeframe for appropriate reporting of adverse events, unanticipated problems, protocol noncompliance and protocol deviations to the IRB, and as applicable the FDA, or the government agency program official or sponsor representative responsible for the grant or contract.
- An explicit statement of risk level determination by the PI. Overall risk assessment associated with the protocol may be assessed by the investigator as minimal, moderate or high. Final determination of the risk level of the study is determined by the IRB.

Additional DSMP Requirements Based on Risk:

4. Minimal Risk Studies

The DSMP for Minimal Risk studies must include:

- Identification of the individual(s) who will be responsible for monitoring the data, assuring protocol compliance, conducting the safety reviews, and the required frequency of the reviews
- Explicit statement of Minimal Risk(s), and, if applicable, a description of any expected adverse events such as bruising or minor infection from a blood draw, or breach of confidentiality; or
- A statement that adverse events are not anticipated
- A plan for reporting to the IRB Reportable Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others at Yale or other sites in accordance with Yale IRB policy, when applicable for multi-center trials.

5. Moderate or High Risk

The DSMP for Moderate or High risk studies must, at a minimum, include:

- Identification of the individual(s) who will be responsible for monitoring the data, assuring protocol compliance, reporting protocol non-compliance, and conducting the safety reviews..
- Identification of the frequency of reviews
- Explicit statement of Moderate or High risk and a description of any expected adverse events.
- Plan for attribution of adverse events, *e.g.* determining whether the event is related to study participation
- Plan for grading adverse events (See 420 GD.1 Data and Safety Monitoring Plan Guidance for grading instructions)
- Plan for reporting Reportable Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others at Yale or other sites, when applicable for multi-center trials, to the IRB.
- Plan for reporting adverse events and unanticipated problems to co-investigators on the study, and, as appropriate, to the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC)), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

420.2 Investigator Responsibilities

The Principal Investigator is required to provide ongoing supervision and evaluation of the activities of the study, including the frequency and severity of adverse events and whether new risks have been identified and whether appropriate progress is being made. The DSMP must describe how the PI will perform the supervision and evaluate the progress of the trial, including periodic assessments of data quality and timeliness, subject recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Ongoing oversight should also involve consideration of factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or the ethics of the study.

Multi-Center Clinical Trials

A Principal Investigator who serves as the sponsor of a multi-center trial has additional responsibilities for coordinating the trial across all sites. These responsibilities include, but are not limited to, ensuring ongoing IRB approval at external study sites, monitoring adverse events and reporting to the IRB, the FDA, the Sponsor, and other bodies that monitor the conduct of the study, and retaining copies of this documentation. A multi-center clinical trial may require a central monitoring entity to perform these functions.

420.3 IRB Responsibilities

The IRB will not approve a protocol without assessing the need for and adequacy of the study's DSMP. The IRB will consider whether all the required elements are included in the DSMP and whether the plan will afford timely and rigorous monitoring relative to the anticipated risks of the research as well as timely notification to the IRB, FDA, other research sites and oversight bodies as applicable.

Related Information

420 GD.1: Data and Safety Monitoring Plan (DSMP) Guidance

420 FR.1: Data and Safety Monitoring Plans Template

IRB Policy 710: Reporting Adverse Events and Unanticipated Problems

710 PR1: Reporting Adverse Events to the IRB

710 PR2: Reporting Unanticipated Problems Involving Risks to Research Subjects or Others to the IRB

710 PR.3: IRB Review of Reports of Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

710 FR1: Unanticipated Problem Involving Risks to Subjects or Others Report Form

710 FR2: Report of Adverse Events under a Yale PI

710 FR3: Report of External Adverse Event(s) (AEs) under a Non -Yale PI

Contacts

Subject	Contact	Phone
Data and Safety Monitoring Plans:	Human Investigation Committees Human Subjects Committee	203-785-4688 ysmhic@yale.edu human.subjects@yale.edu

Roles and Responsibilities

Human Research Protection Program (HRPP)

The Human Research Protection Program is responsible for oversight of human research protection through ongoing education, monitoring, and evaluation of all parties involved in the conduct of human research.

Human Investigation Committees (HIC)

HIC I, HIC II, HIC III and HIC IV serve as the Institutional Review Boards or IRBs for human subjects biomedical research conducted at Yale University.

Human Subjects Committee (HSC)

The HSC serves as the Institutional Review Board or IRB for social, behavioral and educational human research conducted at Yale University

Revision History: 5/30/2007, 11/19/2009. 9/27/2012, 11/5/2012, 5/30/2013, 11Dec2017

References

National Institutes of Health: NIH POLICY FOR DATA AND SAFETY MONITORING (http://grants.nih.gov/grants/guide/notice-files/NOT98-084.html)

National Institutes of Health: FURTHER GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html)

NCI Guidelines at http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines

45 CFR §46.111(a)(6)

21 CFR §56.111(a)(6)